Considerations for the Design of a Systematic Review of Interventions for Preventing Clinical Alzheimer's-Type Dementia, Mild Cognitive Impairment, and Age-Related Cognitive Decline

Letter Report

Committee on Decreasing the Risk of Alzheimer's-Type Dementia, Mild Cognitive Impairment, and Age-Related Cognitive Impairment

Board on Health Sciences Policy

Institute of Medicine

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December 22, 2015

Richard J. Hodes, M.D.
Director, National Institute on Aging
National Institutes of Health
Building 31, Room 5C35
Bethesda, MD 20892

Dear Dr. Hodes:

The National Institutes of Health—and many other organizations and individuals worldwide—are interested in the state of the science on preventing Alzheimer's disease, mild cognitive impairment, and age-related cognitive decline. To develop a better understanding of current scientific evidence, implications for public health messaging, and future research needs, the National Institute on Aging (NIA) turned to the Agency for Healthcare Research and Quality (AHRQ) and the National Academies of Sciences, Engineering, and Medicine (the Academies). Specifically, NIA asked AHRQ to commission and oversee a systematic review of the evidence on interventions to decrease the risk of developing clinical Alzheimer's-type dementia and mild cognitive impairment (MCI), and delay or slow age-related cognitive decline (ARCD). NIA also asked the Academies to convene an expert committee that will provide input into the design of the AHRQ systematic review and, later, use the review to make recommendations that inform public health messaging on preventive interventions and recommendations for future research. This letter report summarizes the committee's input into the design of the AHRQ systematic review. The names of the committee members and their affiliations are listed in Enclosure A, and the committee's statement of task is in Enclosure B.

The Academies committee held a meeting on December 15 and 16, 2015, to provide input on the preliminary key questions and a draft study design prepared by the Minnesota Evidence-based Practice Center (EPC), which AHRQ contracted to conduct the systematic review.[1,2] During the meeting, the committee met in open session with representatives from NIA, AHRQ, and the EPC to discuss the committee's task and the design of the systematic review. Other interested parties had an opportunity to comment as well. The committee also met in

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[1] Minnesota Evidence-based Practice Center. 2015. *Topic refinement: Interventions for preventing cognitive decline and Alzheimer's disease*. Prepared for the Agency for Healthcare Research and Quality. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?topicid=634&search=&pageaction=displaytopic (accessed December 17, 2015).

[2] A note about terms: The committee's original statement of task (see Enclosure B) uses terms and draft key questions that existed during the project initiation stage, but no longer exist. During subsequent work by the Evidence-based Practice Center, these terms and questions evolved, as seen in the key questions on which the committee was asked to comment. In consultation with the National Institute on Aging at the first committee meeting, these terms were further refined to *clinical Alzheimer's-type dementia*, *mild cognitive impairment*, and *age-related cognitive decline*. For clarity, this letter uses these terms; an updated statement of task is currently being formalized.

private to deliberate further. This document summarizes the committee's suggestions for refining the key questions and study design. This letter report was independently reviewed by two external individuals to ensure it meets institutional standards for objectivity, evidence, and responsiveness to the study charge. These individuals are named in Enclosure C.

PUTATIVE INTERVENTION TARGETS

During the December 15 meeting, the EPC asked the Academies committee for advice on intervention targets to include in the search strategy. Box 1 provides a list of putative intervention target categories, along with specific examples. These examples are not intended to be exhaustive; the search may yield additional interventions.

BOX 1
Putative Intervention Targets

Co-Existing Conditions and Associated Interventions

- Blood pressure control (e.g., pre-hypertension and hypertension; medications and non-pharmacologic)
- Depressive symptoms (e.g., pharmacology, behavioral interventions)
- Diabetes prevention and control (e.g., behavioral interventions, medications, insulin)
- Dyslipidemia (e.g., statins, other medications)
- Multiple chronic conditions
- Obesity and weight loss (e.g., obesity prevention, caloric restriction, surgery, medications)
- Sensory impairments (hearing, vision)/interventions

Other Drugs and Supplements

- Aspirin/nonsteroidal anti-inflammatory drugs
- Drugs for memory (e.g., memantine)
- Hormone therapies (e.g., estrogen, selective estrogen receptor modulators, testosterone)
- Medication management (e.g., anticholinergics)
- Nutraceuticals (e.g., gingko biloba, fish oil)
- Vitamins and dietary supplements (e.g., multivitamins, vitamin D)

Lifestyle and Social Support Factors

- Cognitive stimulation and training
- Diet (e.g., Mediterranean, low fat)
- Leisure activities
- Multimodal interventions
- Physical activity (e.g., aerobic, resistance training, balance, sedentary activity)
- Sleep quality and disorders
- Social engagement (e.g., network)
- Substance use (e.g., alcohol, smoking, drugs)

Community Factor

- Built environment (e.g., air pollution, walkability, lead exposure)

The EPC indicated the intent to examine subgroups and potentially interacting factors with respect to intervention effects. The committee agrees that this is important; evidence about *which interventions work for which groups* will be important to the design of future public education efforts. The committee provides responses to the EPC's specific questions on this topic below. In addition, in the interest of testing the influence of the potential modifiers of intervention effects, the committee recommends that the EPC consider coding for and testing the impact of the factors listed in Box 2. Additional factors may emerge during the review process.

BOX 2
Potential Modifiers of Intervention Effects

Population Factors

- Age (middle age, older adults [60 or 65+], younger older adults [60 or 65-85], very old adults [85+])
- Baseline levels of comorbidities (e.g., cardiovascular disease, diabetes, traumatic brain injuries)
- Baseline levels/rates of mutable factors
- Genome (apolipoprotein E [APOE] e4 genotype)
- Marital status
- Personality
- Race and ethnicity
- Residence status
- Sex
- Socioeconomic status, including early education[a]

Methodology Factor

- Independence of evaluation team and intervention development team[b]

[a] There may be a lot of missing data on income.
[b] There is a study quality issue on replicability in the literature assessing impact of cognitive stimulation interventions.

CONSIDERATIONS FOR THE PRELIMINARY KEY QUESTIONS

The EPC proposed a set of four key questions (KQs) to address in the systematic review. Provided below are framing remarks that inform the overall design of the KQs, followed by specific edits and comments on each question.

The natural history that leads to Alzheimer's-type dementia could be summarized as follows: persons with normal cognition start developing deterioration in their cognitive performance of slow onset and progression. When this deterioration achieves a "clinically significant" level of cognitive deterioration that is documented objectively, this level of deterioration may be called cognitive impairment. This cognitive impairment may or may not be accompanied by subjective cognitive complaints. If the cognitive impairment is not accompanied by significant functional impairment (i.e., persons can live independently despite cognitive impairment), the cognitive impairment can be termed *mild cognitive impairment* or *cognitive*

impairment without dementia. If deterioration in cognitive performance continues to the point where a person cannot maintain independence of function, the cognitive impairment is called *dementia*. Given this natural history, cognitive performance is recognized as a patient-centered outcome, in addition to MCI. Thus, the following exploration of outcomes makes sense:

- Among adults without cognitive impairment, relevant outcomes should include (but not be limited to) changes in cognitive performance and in cognitive status (MCI, dementia). Search terms could include cognition, cognitive, dementia, Alzheimer's, age associated cognitive decline, age associated cognitive impairment, subjective cognitive decline, cognitive impairment no dementia, cognitive impairment without dementia.
- Among adults with MCI (cognitive impairment without dementia), relevant outcomes should include (but not be limited to) changes in cognitive performance and incident dementia. Search terms could include cognition, cognitive, dementia, Alzheimer's, age associated cognitive decline, age associated cognitive impairment, subjective cognitive decline, cognitive impairment no dementia, cognitive impairment without dementia.

Certain intermediate biomarkers that have been examined include total brain and hippocampal volumes; white matter hyperintensity volume; uptake with fluorodeoxyglucose positron emission tomography (PET) in key areas of the brain (e.g., temporomedial lobes); accumulation of brain amyloid ascertained with brain PET; and cerebrospinal fluid levels of Tau, phospho-Tau, and amyloid beta. These intermediate biomarkers should be considered as secondary outcomes when available in studies of interventions.

Provided below are specific edits and comments on the KQ language. For conceptual clarity, the committee suggests reordering the first two KQs so the two questions about adults without cognitive impairment are adjacent and the questions progress from the most clinically obvious challenge (clinical Alzheimer's-type dementia) to the less clinically obvious condition (MCI) and then to ARCD.

KQ1 ~~KQ2~~: In adults with mild cognitive impairment, what are the effectiveness, comparative effectiveness, and harms of different interventions for reducing the risk of developing clinical Alzheimer's-type dementia ~~or other neurodegenerative dementias~~?

Do effectiveness, comparative effectiveness, and harms of interventions differ as a function of patient characteristics (including cumulative cognitive insults), including both fixed ~~(gender, age, genetics, education, SES)~~ and potentially modifiable characteristics, considered individually and when present in combination?

Comment: Please see Box 2 for a list of fixed characteristics to consider, the preamble above, and the responses to Questions 1-10 below.

KQ2 ~~KQ1~~: In adults without cognitive impairment, what are the effectiveness, comparative effectiveness, and harms of different interventions for reducing the risk of developing mild

cognitive impairment or clinical Alzheimer's-type dementia ~~or other neurodegenerative dementias~~?[3]

Do effectiveness, comparative effectiveness, and harms of interventions differ as a function of patient characteristics, including both fixed ~~(gender, age, genetics, education, SES)~~ and potentially modifiable characteristics, considered individually and when present in combination?

Comment: Please see Box 2 for a list of fixed characteristics to consider, the preamble above, and the responses to Questions 1-10 below.

KQ3: In adults without cognitive impairment, what are the effectiveness and comparative effectiveness and harms of interventions ~~for reducing the risk of developing~~ that help to maintain cognitive performance and/or delay or slow age-related cognitive decline?

Do effectiveness, comparative effectiveness, and harms of interventions differ as a function of patient characteristics, including both fixed ~~(gender, age, genetics, education, SES)~~ and potentially modifiable characteristics, considered individually and when present in combination?

Comments: Note that the committee modified KQ3. Supporting discussion is included in the preamble above and the responses to Questions 1-10 below. Please also see Box 2 for a list of fixed characteristics to consider.

~~**KQ4: What are the relationships between intermediate outcomes such as cognitive test results, biomarkers, and findings on brain imaging and incidence of mild cognitive impairment or Alzheimer's or other neurodegenerative dementia?**~~

Comment: The deletion of KQ4 is recommended because it is not central to the charge. In addition, the exploration of intermediate outcomes in this field is moving extremely quickly, and it is likely premature to conduct a systematic review of this nature on this topic, particularly because it will be 1.5 years until the project is completed and much will be different in this rapidly changing field.

RESPONSES TO QUESTIONS

In addition to the KQs above, the EPC provided 10 questions on which it hoped to receive advice from the Academies committee. These questions are listed below, along with responses from the committee.

1. How should we handle interactions between immutable risk factors and interventions? We expect that few studies have attempted this, but believe it is a design issue worth noting.

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[3] The underlined text is used to indicate additions to the preliminary key questions provided by the Evidence-based Practice Center and ~~strikethrough~~ is used to indicate deletions.

Response: This is important but, as noted, there may be little data looking specifically at interactions or effects of interactions by subgroups. We would like to see any detail that does appear in the original reports. An exemplar list of factors can be found in Box 2. Interactions could also be present among mutable factors. For example, age may be of particular interest as a potential modifier in interventions related to cardiovascular risk factors. If a main effect is strong, we would value any interactions noted. We would like to see intervention effects combined across studies of different subpopulations where feasible, but levels and potential causes of heterogeneity should be noted.

2. A number of issues concern how we might define subgroups, based on underlying conditions or baseline values.

Response: We would be interested in noting subgroups as defined by the studies, both for interactions among factors and for targeted intervention populations. The list in Box 2 should be instructive. It is also important to remember that duration of exposure to a risk factor, or the stage in the lifespan in which the exposure occurred, or the presence or absence of chronic conditions, could impact the effectiveness of an intervention. An intervention could also have a different effect on persons with MCI versus persons with normal cognition.

3. When we address an intervention targeting a risk factor (e.g., exercise), do we need to consider the baseline value? Again, we anticipate this was rarely done, but should be.

Response: Yes, that would be important to report when available. Regarding baseline values, it would be good to include the studies, describe the population, and code in a manner relevant to the risk factor (e.g., deficient or normal; sedentary, low physical activity, high physical activity; clinically diagnosed condition or not; never smokers, ex-smokers, current smokers). Studies that describe/assess the baseline level of the risk factor are obviously better. Studies that report risk factor trajectory for many years before intervention are even better. Meta-regression could be useful comparing studies. Box 2 includes factors to consider.

4. What is the best way to assess ARCD?[4] How is it related to MCI?

Response: A true assessment of ARCD is challenging. A range of cognitive domains may be included in studies of ARCD, such as memory, attention, executive function, language, and visuospatial processing. It is common for studies to establish an arbitrary cut-off in defining ARCD (e.g., test performance greater than 0.5 or 1.0 standard deviations below the mean of a normative sample, adjusted for age and education). Such definitions can be applied to groups of subjects cross-sectionally, but more commonly longitudinal data are examined to identify changes that exceed those in a normative sample. If ARCD is believed to be part of aging, one would not expect it to evolve into MCI, which is defined as abnormal cognitive decline.

5. Does anyone know of a study of interventions for cumulative insults in Alzheimer's disease?

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[4] Additional discussion is provided in the background section of this document: Minnesota Evidence-based Practice Center. 2015. *Topic refinement: Interventions for preventing cognitive decline and Alzheimer's disease*. Prepared for the Agency for Healthcare Research and Quality. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?topicid=634&search=&pageaction=displaytopic (accessed December 17, 2015).

Response: There are existing studies that address this question indirectly with interventions in multiple domains (e.g., physical activity + cognitive training + diet) or by treating multiple medical conditions (e.g., diabetes, hypertension, dyslipidemia, smoking cessation). An example of an intervention that addresses multiple domains is the FINGER study.[5] An example of an intervention that addresses multiple risk factors is the PreDIVA study.[6]

6. Does anyone know of a study that addresses interventions targeted at interactions of mutable and immutable risk factors?

Response: Yes. A common interaction that might be addressed in the literature is that of APOE e4 and a certain intervention. For example, a study found that cognitive and functional improvements in response to the drug rosiglitazone were only seen in patients with Alzheimer's disease who were APOE e4 negative.[7] A pilot study reports preliminary data that metformin may be efficacious in preventing cognitive decline among persons who are also APOE e4 negative.[8] Another recent study explores the interactions between APOE e4 status and a number of risk factors and interventions.[9]

7. How can we address the problems of confounding and selective attrition that threaten studies with long follow-up periods?

Response: Most studies of interventions targeting Alzheimer's disease outcomes require long follow-up times and are conducted in cohorts of individuals with increasing barriers toward participation in research. Attrition rates may vary from 3 percent to 10 percent or more per year, even in well-conducted studies. Informative censoring (i.e., lost follow-up that is related to cognitive decline and impairment) is to be expected. It is important that studies report rates of lost follow-up, characteristics of participants that are related to lost follow-up, and whether there is evidence of differential retention between intervention groups. There are commonly used statistical approaches to reduce the biases that may be introduced by differential follow-up and to estimate the sensitivity of findings to this phenomenon; studies should be evaluated according to whether they report the results of analyses toward these goals. In addition to reporting rates of attrition, a review should note if there is a report of imputation methods, sensitivity analyses, or other methods.

8. We plan to include studies [that only look at] intermediate outcomes, in addition to those with final health outcomes. What do we do in instances when there is not strong evidence relating the intermediate outcomes to the final health outcomes? What should be the role of modeling?

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[5] Ngandu, T., et al. 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised control trial. *Lancet* 385(9984):2255-2263.

[6] Richard, E., et al. 2009. Prevention of dementia by intensive vascular care (PreDIVA): A cluster-randomized trial in progress. *Alzheimer Disease & Associated Disorders* 23(3):198-204.

[7] Risner, M. E., et al. 2006. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *The Pharmacogenomics Journal* 6:246-254.

[8] Luchsinger, J. A., et al. In press. Metformin in amnestic mild cognitive impairment: Results of a pilot randomized placebo controlled clinical trial. *Journal of Alzheimer's Disease.*

[9] Kaup, A. R., et al. 2015. Cognitive resilience to apolipoprotein E ε4: Contributing factors in black and white older adults. *JAMA Neurology* 72(3):340-348.

Response: We recommend that studies of intermediate outcomes (e.g., biomarkers based on imaging or cerebrospinal fluid) should only be incorporated into studies related to risk of progression, as opposed to being the sole focus of an examination of the evidence. This is consistent with our recommendation that KQ4 should not be a stand-alone emphasis of the report. A number of Phase III intervention studies, for example, used biomarkers as key secondary outcomes with respect to a health outcome, such as slowing of cognitive decline in MCI or mild Alzheimer's disease, and these will be informative. Additionally, Phase II clinical trials that use biomarkers as an intermediate outcome, though likely to be underpowered regarding a health outcome, are also likely to provide useful information.

9. Note: We anticipate that several of the issues we will highlight [in the review] will not be addressed in the extant literature. They will form part of a potential research agenda.

Response: We agree that published studies that address important potential interventions in a compelling fashion may not be available. For example, interventions that target cardiovascular risk factors may have been studied individually but not together and/or clinical Alzheimer's-type dementia or MCI may not have been the primary endpoints. The EPC could examine findings from a number of longitudinal observational studies involving large cohorts (3C, ARIC, CARDIA, CHAP, CHS, Framingham, REGARDS, and Rotterdam, among others). In addition, there are trials currently under way for which the results may not be published within the time frame of the current analysis. An assessment of such ongoing trials in the United States and the European Union (e.g., PreDIVA, SPRINT-MIND, and an NIA-funded exercise trial) would inform any discussion of a potential research agenda.

10. We need guidance about how to define the onset of ARCD. As noted [in the background section of the EPC topic refinement document and in question 4 above] for KQ3, we could alternatively attempt to define an "onset" of ARCD based on the self-report of cognitive concerns (now called subjective cognitive complaints [SCCs]), although there is now some evidence that SCCs are actually associated with increased rates of incident dementia in the years following initial reports. There is not agreement that ARCD is the same as SCCs.

Response: We recommend examining cognitive decline as a continuum. We do not recommend trying to treat ARCD as a condition that has a discrete onset. If an intervention exists in which the subjects are performing within the normal range but have "cognitive complaints," then this study should be included in the literature review.

On behalf of the committee, I express our appreciation for the opportunity to be of service in furthering the study of this critical topic. We hope that you find our comments on the draft AHRQ/EPC KQs and study design to be constructive and we look forward to continuing our service in this important endeavor.

Sincerely,

Alan I. Leshner
Committee Chair

Enclosure A: Committee on Decreasing the Risk of Alzheimer's-Type Dementia, Mild Cognitive Impairment, and Age-Related Cognitive Impairment

Alan I. Leshner (*Chair*), CEO Emeritus, American Association for the Advancement of Science
Marilyn Albert, Professor of Neurology, Director of the Division of Cognitive Neuroscience, Johns Hopkins University School of Medicine
Lisa L. Barnes, Professor of Neurological Sciences and Behavioral Sciences, Director of the Rush Center of Excellence on Disparities in HIV and Aging, Rush University Medical Center
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Eric B. Larson, Vice President for Research, Group Health Executive Director, Group Health Research Institute
José A. Luchsinger, Florence Irving Associate Professor of Medicine, Associate Professor of Epidemiology, Columbia University
Ronald C. Petersen, Director, Alzheimer's Disease Research Center; Director, Mayo Clinic Study of Aging, Mayo Clinic
Ralph L. Sacco, Professor and Olemberg Chair of Neurology, Executive Director of the McKnight Brain Institute, University of Miami; Chief of Neurology, Jackson Memorial Hospital
Sudha Seshadri, Professor of Neurology, Boston University School of Medicine
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Enclosure B: Statement of Task[10]

An ad hoc committee will examine the evidence on preventive factors and/or interventions associated with decreasing the risk of developing Alzheimer's-type dementia, amnestic mild cognitive impairment, and age-related cognitive impairment (i.e., primary prevention) and make recommendations to inform public health strategies and messaging and recommendations for future research. The committee's work will be based on a systematic review commissioned by the Agency for Healthcare Research and Quality (AHRQ) and will take place in two phases: in the first phase the committee will provide input into the design of the AHRQ systematic review and in the second phase the committee will use the review to make its recommendations.

Phase 1:

The committee will convene to inform the development of an AHRQ systematic review that will address the following draft key questions (KQs):

- What are the preventive factors and/or interventions associated with decreasing the risk of developing Alzheimer's-type dementia?
- What are the preventive factors and/or interventions associated with decreasing the risk of developing amnestic mild cognitive impairment?
- What are the preventive factors and/or interventions associated with decreasing the risk of developing age-related cognitive impairment?

Interventions targeting stroke risk factors will be a priority in this study.

Responding to the preliminary KQs and a preliminary study design developed by the National Institutes of Health (NIH), AHRQ, and the Evidence-based Practice Center (EPC) that AHRQ will contract with to conduct the systematic review, the Institute of Medicine committee will provide advisory input to NIH, AHRQ, and the EPC in the form of a short (1-3 page) *data request* document that describes potential changes and considerations for the KQs and study design that would result in a systematic review that would be most informative for the committee's work during phase 2.

Phase 2:

After the AHRQ/EPC systematic review is released, the committee will reconvene to consider the evidence found (based on the final KQs addressed in the systematic review). Interventions targeting stroke risk factors will be included. Based on the AHRQ systematic review and additional expert and public input, the committee will assess the quality of existing evidence and develop a short report that makes recommendations to inform the development of

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[10] A note about terms: The committee's original statement of task, shown here, uses terms and draft key questions that existed during the project initiation stage, but no longer exist. During subsequent work by the Evidence-based Practice Center, these terms and questions evolved, as seen in the key questions on which the committee was asked to comment. In consultation with the National Institute on Aging at the first committee meeting, these terms were further refined to *clinical Alzheimer's-type dementia*, *mild cognitive impairment*, and *age-related cognitive decline.* For clarity, this letter uses these terms; an updated statement of task is currently being formalized.

public health strategies and messaging (i.e., which preventive factors and interventions are supported by sufficient evidence to be incorporated into public health strategies and messages) and recommendations for future research.

The committee will hold an information-gathering workshop open to the public during the course of its work to seek input from stakeholders on the draft AHRQ report. The report will focus on factors and interventions that prevent or reduce the risk of developing Alzheimer's-type dementia, amnestic mild cognitive impairment, and age-related cognitive impairment; it will not focus on identifying risks for developing Alzheimer's-type dementia, amnestic mild cognitive impairment, and age-related cognitive impairment, as this has been the topic of significant previous research.

Enclosure C: Review

This letter report has been reviewed by **Huda Akil,** University of Michigan, and **Enriqueta Bond,** Burroughs Wellcome Fund (emeritus). They were responsible for making certain that this report was carried out in accordance with institutional procedures and meets institutional standards for objectivity, evidence, and responsiveness to the study charge. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.